DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125545

BLA APPROVAL

Hospira, Inc., a Pfizer company
Attention: Tracy Dianis
Director, Global Regulatory Affairs Biologics
275 N. Field Drive, Building H1
Lake Forest, IL 60045

Dear Ms. Dianis:

Please refer to your Biologics License Application (BLA) dated December 16, 2014, received December 16, 2014, and your amendments, submitted under section 351(k) of the Public Health Service Act for Retacrit (epoetin alfa-epbx) injection, 2,000 Units/mL, 3,000 Units/mL, 4,000 Units/mL, 10,000 Units/mL, and 40,000 Units/mL in single-dose vials.

We acknowledge receipt of your resubmissions dated December 22, 2016 and November 17, 2017, which constituted a complete response to our October 16, 2015 and June 21, 2017, respectively, action letters.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 1974 to Hospira, a Pfizer company, Lake Forest, Illinois, under the provisions of section 351(k) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Retacrit (epoetin alfa-epbx) injection. Retacrit is indicated for:

- Treatment of anemia due to
  - Chronic Kidney Disease (CKD) in patients on dialysis and not on dialysis
  - Zidovudine in HIV-infected patients
  - The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy
- Reduction of allogeneic red blood cell (RBC) transfusions in patients undergoing elective, noncardiac, nonvascular surgery.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture epoetin alfa-epbx drug substance at (b) (4) The final formulated drug product will be manufactured, filled, labeled, and packaged at Hospira, Inc., 1776 N. Centennial Drive, McPherson, KS 67460. You may label your product with the proprietary name, Retacrit, and market it in 2000, 3000, 4000, 10,000, and 40,000 Units/mL single dose vial for injection.

DATING PERIOD

The dating period for Retacrit shall be 30 months for the 2000, 3000, 4000, and 10,000 U/mL strengths and 24 months for the 40,000 U/mL strength from the date of manufacture when stored at 5 ± 3 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at ≤ (b) (4) °C.

We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Retacrit to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Retacrit, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide, Instructions for Use). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "*SPL Standard for Content of Labeling Technical Qs and As*" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on May 4, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved BLA 125545**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are granting partial waiver of pediatric study requirements for the following indications and related age groups, since the necessary studies are impossible or highly impracticable.

- For anemia due to chronic kidney disease (CKD) in patients on dialysis and not on dialysis, partial waiver for patients 0 to <1 month old
- For anemia due to concomitant myelosuppressive chemotherapy, partial waiver for patients 0 to <5 years old
- For anemia due to Zidovudine in HIV-infected patients, partial waiver for patients 0 to < 8 months

For reduction of allogeneic red blood cell transfusions in patients undergoing elective, non-cardiac, nonvascular surgery, full waiver for studies for age group 0 to 18 years, because the necessary studies would be impossible or highly impracticable.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

PMC 3403-1 Complete a storage verification study for the (b) (4) used in the epoetin alfa-epbx drug substance manufacturing process during (b) (4)

The timetable you submitted on April 30, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2018
Study/Trial Completion:	12/2020
Final Report Submission:	06/2021

PMC 3403-2 Establish in-process action limits for (b) (4) (b) (4) (b) (4) drug product by June 2019 based on the number of batches produced by that date.

The timetable you submitted on April 30, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2018
Study/Trial Completion:	06/2019
Final Report Submission:	07/2019

PMC 3403-3 Repeat the endotoxin spike recovery study for two additional lots of 40,000 U/mL drug product (b) (4) to demonstrate reproducible endotoxin recovery of at least (b) (4) theoretical spike level. Include intermediate time points to obtain at least two consecutive and consistent data points for analysis (day 0, 3, 5, 7 is recommended).

The timetable you submitted on April 30, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/2018
Study/Trial Completion:	08/2018
Final Report Submission:	09/2018

Submit clinical protocols to your IND 100685 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Acting Deputy Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROMEO A DE CLARO
05/15/2018